AWARD NUMBER: W81XWH-16-1-0300

TITLE: Metformin Therapy for Fanconis Anemia

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REPORT DATE: August 2017

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
August 2017	Annual	1 Aug 2016 - 31 Jul 2017

4. TITLE AND SUBTITLE

Metformin Therapy for Fanconis Anemia

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-16-1-0300

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This award pertains to the treatment of the inherited bone marrow failure syndrome Fanconi's Anemia. Specifically, the commonly used diabetes drug metformin will be tested by itself and in combination with the current standard of care, anabolic steroids.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	7	19b. TELEPHONE NUMBER *(include area code)*

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1. Introduction

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2. Keywords

Fanconi Anemia, bone marrow failure, treatment, drug, small molecule, DNA damage, metformin

3. Accomplishments

We started work on this project less than a year ago and already have made good progress.

Major Goals:

Specific Aim 1: To evaluate metformin for the treatment of FA

Metformin is a biguanide drug widely used for the treatment of type 2 diabetes. In humans, it is known to have cancer chemoprevention properties. We found that MET enhances hematopoiesis specifically in *Fancd2*-/- mice, but how it does so is unclear. Here, we will determine whether MET acts via AMPK activation or as an aldehyde scavenger. We will ascertain whether it can prevent inflammation-induced anemia and whether it is beneficial when BMF has already started.

Specific Aim 2: To evaluate the combination of anabolic androgens with metformin for the treatment of FA.

Many FA patients respond to androgens by significant improvement of their blood counts8. We now understand how androgens work and predict that there is no overlap with the mechanism of action of MET. Androgen therapy does not cure FA and we will therefore determine whether the combination of oxymetholone with metformin can synergistically improve hematopoiesis in FA.

Goals achieved:

Specific progress has been made on both Aims.

For Aim 1, we have generated a cohort of Fancd2 mutant mice to be aged until they display bone marrow failure. We plan to determine whether metformin can reverse already established anemia. Anemia developments takes 12-18 months from birth and hence the metformin treatment will start at that time, during year 2 of the grant.

We have also started a cohort of Fancd2/Aldh2 double mutant mice to address the question of whether metformin can directly scavenge aldehydes. In addition, we have generated some human Fanconi cell lines deficient in aldehyde metabolism to perform in vitro experiments in parallel.

Aim 2 has a timeline of over one year and generating the mice required to populate the project took considerable time, but has now been accomplished. We have populated four cohorts of FA mutant mice: 1) Mice receiving both oxymetholone and metformin; 2) mice receiving metformin alone; 3) mice receiving oxymetholone alone and 4) controls, receiving placebo (no drug). The experiments are ongoing. No overt side effects of the combination therapy have been seen.

Training opportunities:

Nothing to report.

Results dissemination:
Nothing to report.

P**lans for the next reporting period:**
We are pretty much on track of the timeline described in our application. A lot of experimental animals need to be generated by breeding and then aged from 6-18 months. Breeding efficiencies are only ¼ (recessive disease) and populating our study cohorts simply takes time. Hence, most of the experimental readouts will come in year 2 of the grant. We will complete Aim 2 and do a comprehensive analysis of the hematopoietic effects of combination therapy. The long term treatment will continue for another 9 months before analysis takes place.
For completion of Aim 1, we need to generate a cohort of FA mice with already established bone marrow failure. These mice have been generated and now simply have to be aged. Despite our finding that metformin can in fact detoxify aldehydes, we will nonetheless complete our experiments aimed as assessing the role of AMPK activation.

4. Impact

Principal discipline:
Metformin has never been considered for the treatment of bone marrow failure before. Our preclinical data in mice are sufficiently compelling that a clinical trial of children with Fanconi Anemia with metformin is being implemented at Boston Childrens Hospital. The planned start date is January 2018.

Other disciplines:
Although hundreds of papers have been written about metformin and although many cancer prevention clinical trials are ongoing, metformin has never before been reported to block DNA damage and enhance genome integrity. The aldehyde scavenging effects of metformin have also not been previously reported. We believe that our findings provide a potential mechanism for the cancer prevention effects of metformin. This is a novel paradigm in the field.

Technology transfer:
Nothing to report.

Society:
Nothing to report.

5. Changes

Nothing to report.
We are happy to report that our experimental plans are coming off without a hitch and are on time.

6. Products

Spanish Fanconi Anemia Society Meeting, Madrid, Spain, June 2017: “Small Molecule Therapy of Fanconi Anemia”. Author: M. Grompe

Web-sites:
Nothing to report

Technologies:
Nothing to report

Inventions/patents:
Nothing to report

7. Participants and other collaborating organizations.

Individuals on the project

Name	*Markus Grompe, M.D.*
Project Role	*Principal investigator*
Researcher ID	*0000-0002-6616-4345*
Person month worked	*1*
Contribution	*Overall experimental design. Oversight of project personnel; communication with funding agencies; manuscript writing.*
Funding support	
Name	*Qingshuo Zhang, Ph.D.*
Project Role	*Senior Research Associate*
Researcher ID	
Person month worked	*9*
Contribution	*Dr. Zhang is the project leader in the lab; He designs most experiments (in collaboration with Dr. Grompe), performs experimentation himself, collects data and oversees the research assistants working on the project.*
Funding support	
Name	*Leslie Wakefield*
Project Role	*Research Assistant*
Researcher ID	
Person month worked	*3*
Contribution	*Ms. Wakefield is in charge of our mouse animal colony (breeding, genotyping etc.) and assists Dr. Zhang with hands on experimentation.*
Funding support	

Name	*Sean Nygaard*
Project Role	*Laboratory Manager*
Researcher ID	
Person month worked	*1*
Contribution	*Mr. Nygaard is in charge of overall lab organization, including order supplies, equipment maintenance, compliance (animal care).*
Funding support	

Changes:
Nothing to report

Other organizations:
Nothing to report.

8. Special Reporting Requirements

Nothing to report.

9. Appendices

Nothing to report